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Identification of hub genes and enriched pathways in renal ischemia–reperfusion injury via integrative transcriptomic and network analysis

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ABSTRACT

Aims: This study aimed to identify key genes and pathways involved in the pathogenesis of renal ischemia–reperfusion injury (IRI)-induced acute kidney injury (AKI) using an integrative bioinformatics approach.

Methods: Publicly available gene expression profiles from two independent rat kidney microarray datasets (GSE27274 and GSE58438) were analyzed to identify differentially expressed genes (DEGs) between IRI and control groups. DEGs with an adjusted p-value <0.05 and |log2 fold change| >1 were considered significant. Common DEGs from both datasets were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. Protein–protein interaction networks were constructed using STRING and cytoscape, and hub genes were identified with the maximal clique centrality algorithm via the CytoHubba plugin.

Results: A total of 189 overlapping DEGs were identified (117 upregulated, 72 downregulated). Upregulated DEGs were enriched in pathways associated with glutathione metabolism and oxidative stress response, while downregulated DEGs were associated with DNA replication and inflammatory signaling. Hub genes for upregulated DEGs included Gclc, Gclm, Anpep, and Gss, while downregulated hub genes included Mcm2, Gins1, Pcna, and Tnf. These genes represent potential regulatory nodes in the renal IRI response.

Conclusion: This study highlights redox regulation, amino acid metabolism, immune modulation, and cell cycle arrest as major components in the molecular pathogenesis of renal IRI. The identified hub genes may serve as potential diagnostic biomarkers and therapeutic targets. These findings provide a framework for future experimental validation and drug development efforts in AKI caused by IRI.

Keywords: Acute kidney injury, ischemia-reperfusion injury, hub genes, oxidative stress, bioinformatics

INTRODUCTION

Ischemia-reperfusion injury (IRI) is a pathological process involving the temporary reduction and subsequent restoration of blood flow to an organ, which exacerbates cellular dysfunction.[1] During ischemia, cells in the tubular epithelium and outer medulla undergo apoptosis and necrosis. Key pathways such as Notch, PI3K/Akt, TGF-β, NF-κB, bone morphogenetic protein (BMP), TLR4/TRIF and hepatocyte growth factor/mesenchymal-epithelial transition factor (HGF/c-Met), and Wnt have been identified as playing a vital role in IRI. IRI injury constitutes the primary cause of intrinsic acute kidney injury (AKI). Because there is an absence of effective treatments, a significant proportion of patients suffer fatal outcomes (50%) as a result of IRI-induced AKI. Moreover, it exerts a considerable effect on the increased burden of end-stage renal disease.[2] Dialysis and kidney transplantation are the standard treatments for kidney failure today. Nevertheless, dialysis is an expensive and time-consuming process that diminishes the patient's quality of life. Advances in bioinformatics and systems biology offer new perspectives for exploring therapeutic targets. The development of effective therapeutic interventions is hindered by the limited understanding of the intricate mechanisms underlying IRI. A lot of studies have demonstrated that a number of pathways, genes and cellular networks have the capacity to impact the source and development of IRI. In recent years, molecular biology and drug discovery have seen a huge increase in the use of molecular dynamics simulations.[3] This information is crucial for understanding the structure-function relationship of the target, as well as the essence of protein-ligand and gene-to-gene interactions. It can also guide the process of discovering and designing drugs. The emergence of genomics

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and proteomics has led to the identification of many significant targets in human diseases.[4]

In recent years, bioinformatics has enabled the identification of key gene networks in complex renal pathologies including IRI. It involves sifting through large amounts of molecular and clinical data using data mining, pathway analysis, statistical analysis and visual processing.[5] Innovative treatments have been made possible by the elucidation of disease mechanisms. This approach is widely used in disease research.

We expect our study to provide information about the relationships between new biomarkers and pathways, as well as the proteins and genes associated with these pathways, and the possible molecular mechanisms underlying renal IRI. By integrating gene expression data from two independent rat kidney microarray datasets, we aimed to identify differentially expressed genes (DEGs) associated with renal IRI. Through functional enrichment and protein–protein interaction (PPI) network analyses, we sought to uncover key biological processes and signaling cascades that are activated or suppressed in response to IRI. Furthermore, by determining central hub genes within these networks, we aimed to highlight potential diagnostic biomarkers and therapeutic targets that may contribute to a better understanding of the molecular pathogenesis of IRI-induced AKI.

METHODS

Ethics

This study does not contain any clinical or experimental research data obtained directly from human participants or animal subjects by the author. All data in this study were obtained from publicly available databases. The author of this article declares that the materials and methods used in their research did not require ethics committee approval and/or any special legal permission.

Data Collection

Publicly available transcriptomic data were obtained from the Gene Expression Omnibus (GEO) database using two microarray datasets: GSE27274 and GSE58438. Both datasets were derived from Rattus norvegicus kidney tissue samples subjected to IRI or sham operation (control). The first dataset, GSE27274, includes 3 control and 3 IRI rat kidney samples, while the second dataset, GSE58438, contains 5 control and 4 IRI samples. In both datasets, kidney tissues were collected 24 hours after the reperfusion phase. The platforms used along with the number of samples are summarized in Table 1.

Table 1. Summary of GEO datasets used in this study

GEO access number	Control	IRI	Platform
GSE27274	3	3	GPL6101 Illumina ratRef-12 v1.0 expression beadchip
GSE58438	5	4	GPL11534 [RaGene-1_1-st] Affymetrix Rat Gene 1.1 ST Array [transcript (gene) version]

GEO: Gene Expression Omnibus, IRI: Ischemia–reperfusion injury

DEG Analysis

DEGs between IRI and control groups were identified using the GEO2R tool, an R-based online analysis platform integrated within the NCBI GEO database.[6] Two independent microarray datasets (GSE27274 and GSE58438) were analyzed separately (quantile normalization automatically performed by GEO2R platform). Genes with an adjusted p-value <0.05 (FDR-corrected using Benjamini–Hochberg method) and an absolute log2 fold change (|log2FC|) >1 were considered statistically significant. Common DEGs across both datasets were identified using Venn diagram using the online tool Venny 2.1 and used in downstream functional and network analyses. Online platform SRplot is used to form volcano plot graphics.[7]

Gene Ontology and Pathway Enrichment Analysis

Following the identification of DEGs, functional enrichment analysis was performed to gain insight into their potential biological roles. Gene Ontology (GO) annotation including biological process (BP), cellular component (CC), and molecular function (MF) as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were carried out using the DAVID 2021 database.[8] A p-value of less than 0.05 was considered statistically significant for enrichment. Among the results, the top 10 most significantly enriched GO and KEGG pathways were selected for further interpretation and presentation. Visualization of the enrichment results was conducted using SRplot, where enrichment bubble plots were generated to present the enriched categories.

PPI Network Construction and Hub Gene Identification

To investigate the interactions among DEGs, PPI networks were constructed separately for upregulated and downregulated gene sets. The STRING database (https://string-db.org/) was used to generate interaction networks, setting the minimum required interaction score to 0.7 (high confidence). The resulting interaction data were imported into Cytoscape software (version 3.10) for visualization and further network analysis.[9] CytoHubba plugin was utilized to identify hub genes based on the maximal clique centrality (MCC) algorithm.[10] The top 10 hub genes were determined separately for the upregulated and downregulated gene sets. These key genes, representing the most highly interconnected nodes in the network, were considered potential central regulators in the pathophysiology of renal ischemia–reperfusion injury.

RESULTS

DEG Analysis

Differential expression analysis was performed separately for each dataset to identify genes that were significantly altered in response to renal IRI compared to control samples. In the GSE27274 dataset, a total of 730 DEGs were identified, comprising 402 upregulated and 328 downregulated genes. Similarly, analysis of the GSE58438 dataset revealed 1,021 DEGs, including 523 upregulated and 498 downregulated genes. The distribution of DEGs in both datasets is visualized using volcano plots in Figure 1. Top 10 DEGs for GSE27274 and GSE58438 are given in Table 2.

To determine the most robust gene expression changes, the DEG lists from the two datasets were compared, and common

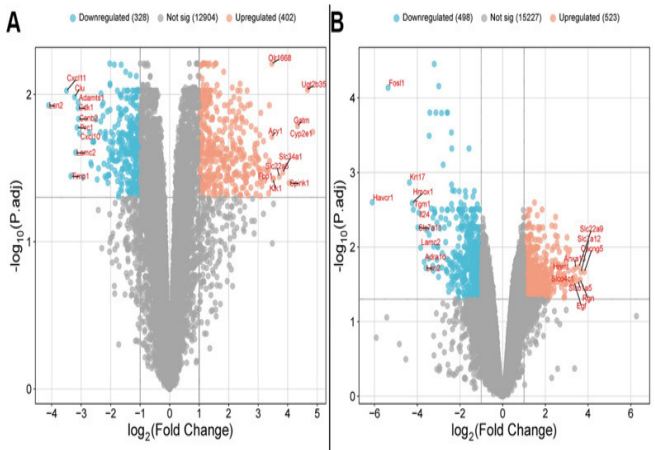

Figure 1. Volcano plots of DEGs (control vs IRI) in the (**A**) GSE27274 and (**B**) GSE58438 datasets
DEGs: Differentially expressed genes

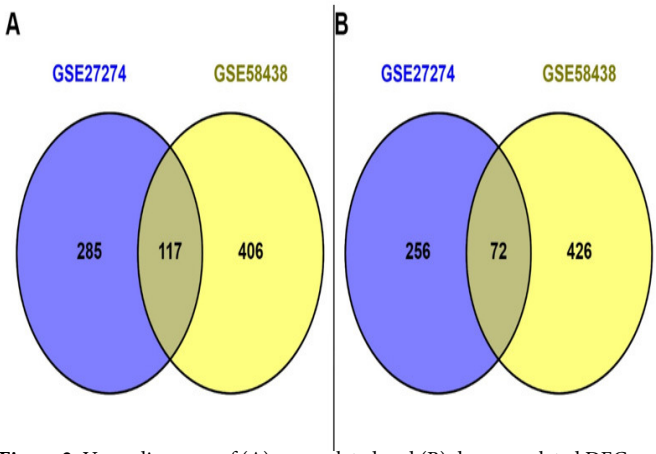

Figure 2. Venn diagrams of (A) upregulated and (B) downregulated DEGs
DEGs: Differentially expressed genes

DEGs were extracted. A total of 189 overlapping DEGs were identified, consisting of 117 commonly upregulated and 72 commonly downregulated genes. The overlap of upregulated and downregulated genes across the datasets is illustrated with a Venn diagram in **Figure 2**. These common DEGs were used in subsequent functional enrichment and network-based analyses.

Functional Enrichment Analysis

GO and KEGG pathway enrichment analyses were performed separately for the upregulated and downregulated common DEGs. GO analysis was conducted across three categories: BP, CC and MF. KEGG pathway analysis was used to identify the most relevant signaling and metabolic pathways associated with the gene expression changes. The top 10 significantly enriched GO terms and KEGG pathways for each gene set are presented as bubble plots in **Figure 3**.

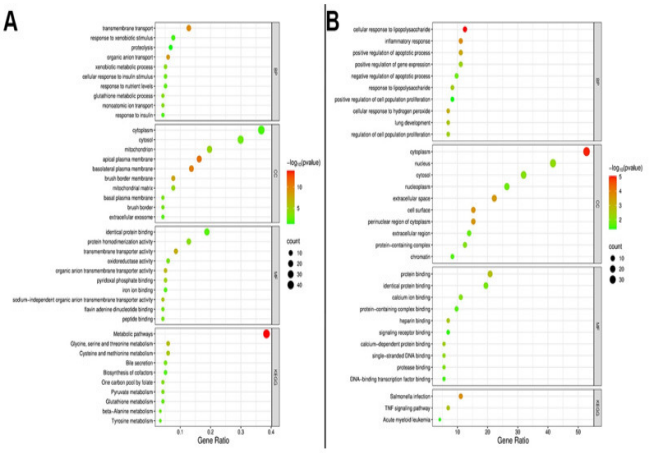

Figure 3. Bubble plots representing the top 10 enriched GO terms and KEGG pathways. (**A**) Upregulated genes (**B**) Downregulated genes.
GO: Gene Ontology, KEGG: Kyoto Encyclopedia of Genes and Genomes, BP: Biological process, CC: Cellular component, MF: Molecular function

Protein–Protein Interaction Network Analysis and Identification of Hub Genes

The common upregulated (117 genes) and downregulated (72 genes) DEGs were analyzed separately to construct PPI networks. Each gene set was uploaded to the STRING database (https://string-db.org/) with a minimum required interaction score of 0.7, and the resulting interaction data were imported into Cytoscape software for network visualization and analysis.

The PPI network for the upregulated genes consisted of 126 nodes and 131 edges, while the network for the downregulated

Table 2. Top 10 DEGs for GSE27274 and GSE58438

GSE27274				GSE58438			
Upregulated		**Downregulated**		**Upregulated**		**Downregulated**	
Gene	**Log2FC**	**Gene**	**Log2FC**	**Gene**	**Log2FC**	**Gene**	**Log2FC**
Cyp2e1	4.852	Lcn2	-4.105	Cacng5	3.829	Havcr1	-6.108
Gatm	4.335	Cxcl11	-3.495	Slc7a12	3.669	Fosl1	-5.365
Ugt2b35	4.155	Timp1	-3.351	Rgn	3.637	Krt17	-4.366
Spink1	4.050	Clu	-3.225	Slc22a9	3.576	Hmox1	-4.235
Slc34a1	3.838	Lamc2	-3.190	Slco1a5	3.535	Tgm1	-4.183
Slc22a6	3.718	Prc1	-3.143	Slc7a3l1	3.535	Slc7a11	-3.971
Fbp1	3.521	Adamts1	-3.106	Anxa13	3.422	Il24	-3.928
Klk1	3.504	Cdk1	-3.103	Slco4c1	3.398	Lamc2	-3.840
Acy1	3.466	Ccnb2	-3.090	Egf	3.356	Adra1d	-3.677
Olr1668	3.464	Cxcl10	-3.051	Hnmt	3.304	Lcn2	-3.596

DEGs: Differentially expressed genes

genes contained 81 nodes and 69 edges. Using the Network Analyzer plugin, the degree values of each node were calculated. In the visualized networks, node color represented the degree value, and edge thickness reflected the combined interaction score between proteins (**Figure 4**).

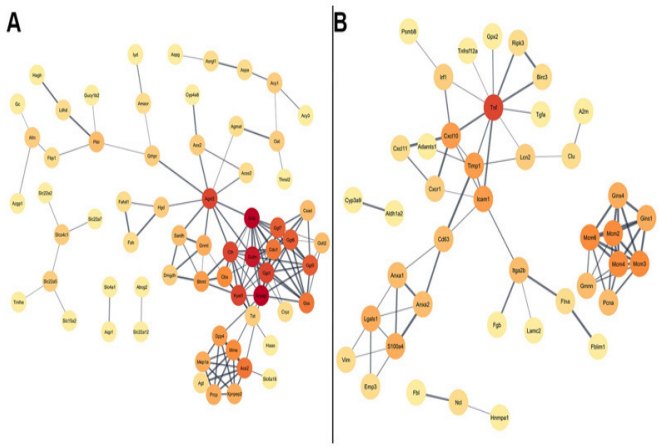

Figure 4. PPI networks of common DEGs. Node color reflects the degree of connectivity; edge thickness indicates interaction confidence. (**A**) Upregulated DEGs (**B**) Downregulated DEGs.
DEGs: Differentially expressed genes

To identify central regulatory components in the networks, the CytoHubba plugin was used to calculate node centrality using the MCC algorithm. The top 10 hub genes were identified for each group. For the upregulated genes, the hub genes included Gclc, Gclm, Anpep, Ggct, Ggt6, Ggt7, Ggt5, Gss, Cth, and Kyat1. For the downregulated genes, hub genes were Mcm2, Mcm3, Mcm4, Mcm6, Gins1, Gins4, Pcna, Gmnn, Tnf, and Cxcl10 (**Figure 5**). These hub genes demonstrated high connectivity within their respective networks and may serve as key regulators in the molecular mechanisms underlying IRI. All the data used in analyses and formation of visuals are given as supplementary material.

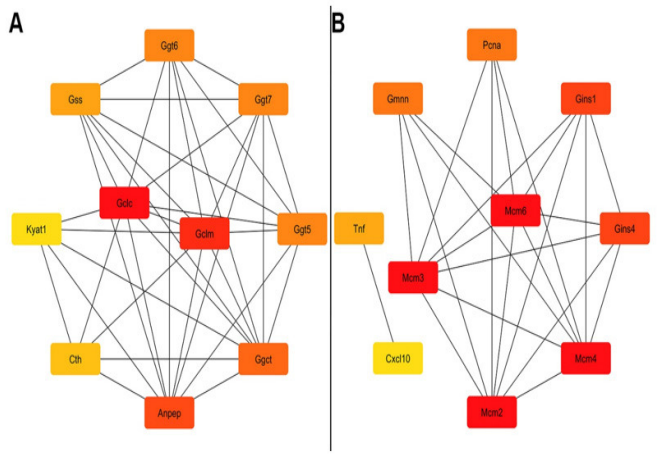

Figure 5. Top 10 hub genes identified by MCC algorithm using CytoHubba. Node color reflects the degree of connectivity. (**A**) Upregulated hub genes (**B**) Downregulated hub genes.
MCC: Maximal clique centrality

DISCUSSION

This study provides novel insight into the redox and cell cycle mechanisms underlying renal IRI-induced AKI through integrated transcriptomic analysis. Renal IRI-induced AKI causes a lot of problems because of its complicated molecular pathogenesis and lack of drugs for treatment.[11,12] The present study used bioinformatics techniques to determine strong gene expression profiles as well as important regulatory molecules in AKI resulting from renal IRI. By integrating two independent rat microarray datasets 117 upregulated and 72 downregulated genes were identified. This approach of using two data sets helps to reduce bias and therefore increases the validity of the stated targets at the biological level.

Functional enrichment analysis revealed that upregulated genes were strongly associated with transmembrane transport, glutathione metabolism, and amino acid-related metabolic pathways. Such findings are in line with the known implication of oxidative stress in renal IRI.[13] Glutathione metabolism plays a central role in neutralizing reactive oxygen species (ROS) and several key enzymes involved in this pathway were among the upregulated hub genes, including Gclc, Gclm, Gss, and Ggct.[14] In particular, Gclc (glutamate-cysteine ligase catalytic subunit) and Gclm (modifier subunit) catalyze the rate limiting step in glutathione biosynthesis and are essential for maintaining redox homeostasis in renal tubular cells.[14,15] The gamma-glutamyl transferases (Ggt5, Ggt6, Ggt7) were also found to be overexpressed indicating increased glutathione turnover most probably aimed at meeting high antioxidant needs or aiding in detoxification.[16] Numerous studies have explored the role of N-acetylcysteine (NAC), a known glutathione precursor in both experimental and clinical cases of AKI whereby it may increase intracellular glutathione levels, lower ROS, and ameliorate tubular recovery.[17] On top of that, sulforaphane is a dietary isothiocyanate present in cruciferous vegetables that can induce the Nrf2 pathway and increase Gclc as well as Gclm expression to provide an alternative way of enhancing antioxidant defense mechanisms.[18]

In case of an injury, there is a metabolic response which changes how amino acids are used by the body, as indicated by the increased expression of certain genes like Anpep (alanyl aminopeptidase), Cth (cystathionine gamma-lyase) and Kyat1 (kynurenine aminotransferase).[19,20] Cth, for instance, is a vital enzyme in H_2S biosynthesis, with H_2S being known to cause vasodilatory, anti-inflammatory as well as cytoprotective effects in renal IRI models.[21] Exogenous administration of H_2S donors, such as NaHS (sodium hydrosulfide) has demonstrated renoprotective properties by reducing apoptosis and preserving mitochondrial function.[22] Likewise, modulation of the kynurenine pathway via kynurenine 3-monooxygenase (KMO) inhibitors, such as Ro 61-8048, has been shown to decrease inflammation and oxidative stress

in other organ injury models and could be explored in the context of renal IRI.[23]

In contrast, downregulated genes were enriched in pathways related to inflammatory responses, lipopolysaccharide signaling, and cell cycle regulation. Interestingly, several central components of the DNA replication machinery such as Mcm2–6, Gins1, Gins4, and Pcna were identified as downregulated hub genes. This suggests that there could be failure or slowing down of tubular epithelial cell proliferation and repair process following injury. At the onset of AKI, arresting the cell cycle is believed to provide protection by stopping injured cells from going through mitosis; nevertheless, an extended arrest might impede recovery and promote fibrosis.[24] Recent studies have identified epigenetic modifiers as potential tools to enhance renal regeneration. For instance, histone deacetylase (HDAC) inhibitors such as valproic acid and trichostatin A have been shown to promote renal repair by modulating chromatin accessibility and activating pro-survival gene programs.[25]

Additionally, it was observed that two highly publicized inflammation mediators, Tnf and Cxcl10, also identified as downregulated hub genes. Although surprising, this may reflect the resolution or suppression phase of inflammation at the 24-hour post reperfusion time point.[26] On the other hand, it might mean that there is some local control over pro-inflammatory signals. It is important to note that TNF blockers like etanercept have been tested in animal models of AKI where they showed partial success in protecting against renal injury; however, their use in real patients is still uncertain.[27]

The analysis of the entire PPI network revealed that upregulated and downregulated genes give rise to distinct but closely linked subnetworks. Specifically, upregulated genes created a network closely related to redox and solute transport, while downregulated genes were most closely linked with DNA replication and immune regulation. These complementary networks reflect the dual nature of AKI pathology involving both injury induced stress responses and suppression of regenerative or immune processes.[28]

Even though some of the identified hub genes are known to play a role in renal injury, others like Kyat1, Ggt7, or Gins4 remain poorly understood and require further investigation. Moreover, it might be possible to use the identified gene networks for drug repositioning strategies. For instance, bardoxolone methyl, an activator of Nrf2, could potentially upregulate key antioxidant genes like Gclc and Gclm, while CDK inhibitors could theoretically modulate Mcm- or Gins-associated pathways involved in cell cycle regulation.[29,30] We predicted that drugs or molecular compounds might regulate hub genes, which could be used as a potential drug to protect against IRI-AKI.

Limitations

Although this approach combines two independent data sets and uses advanced bioinformatics tools, there are some limitations in this research. First, the analyses were based on publicly available microarray data from rat models, which may not fully capture the complexity of human renal IRI. Second, post-transcriptional regulation, protein activity, and cell-specific expression dynamics could not be assessed. Lastly, even though several potential drugs were proposed based on literature and pathway analysis, their ability to modulate the identified hub genes and improve renal outcomes needs to be confirmed through vivo or vitro experiments.

CONCLUSION

This study identified robust and biologically relevant differentially expressed genes in a rat model of renal IRI using integrative transcriptomic and network analysis. The findings point to critical roles for glutathione metabolism, oxidative stress regulation, cell cycle arrest, and immune modulation in the pathophysiology of IRI-induced AKI. Hub genes such as Gclc, Gclm, Mcm2, and Tnf may serve as promising biomarkers or therapeutic targets. Furthermore, bioactive compounds such as NAC, sulforaphane and bardoxolone methyl are some bioactive chemicals that could be introduced in future experimental models as potential therapeutic agents targeting these pathways. These results offer valuable information towards understanding the problem better and may help create new ways of treating IRI-induced AKI in future.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval is not required as this study does not involve any clinical or experimental research data obtained directly from human participants or animal subjects.

Informed Consent

Written informed consent is not required as this study does not involve any clinical or experimental research data obtained directly from human participants or animal subjects.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author reports no conflicts of interest in this work.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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